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ORIGINAL REPORT

Response to Neoadjuvant Systemic Therapy for Breast Cancer in *BRCA* Mutation Carriers and Noncarriers: A Single-Institution Experience

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See accompanying editorial on page 3724; listen to the podcast by Dr. Tung at www.jco.org/podcast

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ABSTRACT

Purpose
To compare the pathologic complete response (pCR) rate and relapse-free survival (RFS) and overall survival (OS) after neoadjuvant systemic chemotherapy (NST) in patients with breast cancer with and without deleterious *BRCA1* and *BRCA2* mutations.

Patients and Methods
A total of 317 women who underwent *BRCA* genetic testing and were treated with NST for breast cancer between 1997 and 2009 were included in the study. The Kaplan-Meier product-limit method was used to estimate RFS and OS rates. Logistic regression models were fit to determine the associations between *BRCA* status, pCR, and survival.

Results
Fifty-seven (18%) and 23 (7%) patients had *BRCA1* and *BRCA2* mutations, respectively. Twenty-six (46%) of 57 *BRCA1* carriers achieved a pCR, compared with three (13%) of 23 *BRCA2* carriers and 53 (22%) of 237 *BRCA* noncarriers ($P < .001$). In the multivariate logistic model, *BRCA1* status (odds ratio [OR] = 3.16; 95% CI, 1.55 to 6.42; $P = .002$), estrogen receptor (ER) negativity (OR = 1.96; 95% CI:1.05 to 3.65; $P = .03$) and concurrent trastuzumab use (OR = 4.18; 95% CI, 2.04 to 8.57; $P < .001$) remained as independent significant predictors for a pCR. At a median follow-up of 3.2 years, 69 patients (22%) experienced a disease recurrence or death. No significant differences were noted in survival outcomes with respect to *BRCA* status and type of NST received. However, among *BRCA1* carriers, patients who achieved a pCR had better 5-year RFS ($P = .001$) and OS ($P = .01$) rates than patients who did not.

Conclusion
BRCA1 status and ER negativity are independently associated with higher pCR rates in patients with breast cancer. Overall prognosis of breast cancer in *BRCA* carriers is similar to sporadic breast cancers.

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INTRODUCTION

Approximately 5% to 10% of all breast cancers are hereditary.[1,2] Known mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2* account for more than 50% of these hereditary breast cancers.[3] Carriers of heterozygous germline mutations in the *BRCA1* or *BRCA2* genes have approximately a 2% to 3% yearly risk of developing breast cancer.[4,5] Several reports have demonstrated that *BRCA1*-associated breast cancer has distinctive histopathologic features compared with sporadic breast cancer. It is usually high grade, poorly differentiated, infiltrating ductal carcinoma; does not express the estrogen receptor (ER) or progesterone receptor (PR); and does not overexpress human epidermal growth factor receptor-2 (HER2).[6-8]

Preclinical studies have suggested that lack of functioning BRCA1 or BRCA2 protein functioning may result in differential treatment response to several chemotherapeutic drugs, which might be explained by distinct pathologic features and gene expression profiles in hereditary breast cancer compared with sporadic cancer.[9-11] Although several studies have reported a profound hypersensitivity to apoptosis in *BRCA1*- and/or *BRCA2*-deficient

breast cancer cell lines when treated with potent inhibitors of the enzyme poly (ADP-ribose) polymerase,[12-14] mitoxantrone, etoposide, cisplatin, and doxorubicin,[15-18] unfortunately there is no consensus regarding the most effective chemotherapy regimen in *BRCA* mutation carriers. Furthermore, data on the effectiveness of neoadjuvant systemic chemotherapy (NST) in *BRCA*-associated breast cancer is limited because of small patient numbers and lack of prospective studies. Likewise, it is still unclear whether achieving a pathologic complete response (pCR) is early predictive of improved long-term survival in *BRCA*-associated breast cancers, as has been demonstrated in sporadic breast cancers.[19-21] Therefore, we conducted this retrospective analysis to determine the efficacy of NST for breast cancer in *BRCA* mutation carriers and noncarrier controls. Our primary objective was to compare the pCR rates with anthracycline- and/or taxane-containing NST regimens between the three study cohorts. Secondary end points included recurrence-free survival (RFS) and overall survival (OS).

PATIENTS AND METHODS

Patient Population

The prospectively maintained Breast Cancer Management System research database of The University of Texas MD Anderson Cancer Center (MDACC) identified 1,809 women with breast cancer who underwent clinical genetic testing for *BRCA1* and *BRCA2* germline mutations between 1997 and 2009. Of 1,809 patients, 317 received NST. Of the 317 women included in our analysis, 237 tested negative for mutations in the *BRCA1* and *BRCA2* genes (hereafter "noncarriers"), 57 were found to carry a *BRCA1* mutation, and 23 *BRCA2* mutation (hereafter "carriers"). Patients with *BRCA* variants of uncertain significance or metastatic disease or whose pathologic response data were not available were excluded from the analysis. Initial clinical stage of all patients was reviewed and based on the seventh edition of the American Joint Committee on Cancer staging criteria.[22] This study was approved by the institutional review board at MDACC. The retrospective analysis of prospectively collected data included patient demographics, tumor characteristics, initial clinical stage, type of NST received, pathologic stage, and recurrence and survival information.

Pathologic Assessment

All pathologic specimens were reviewed by designated breast pathologists at MDACC, and the reports were entered in a prospective research database. Invasive carcinoma was confirmed on initial core biopsy specimens. Histologic type and tumor grade were defined according to the WHO classification system[23] and the modified Black's nuclear grading system,[24] respectively. Immunohistochemical analysis was used to determine ER and PR status. Nuclear staining $\geq$ 10% of either ER or PR was considered strongly positive. HER2 positivity was defined as 3+ receptor overexpression by immunohistochemical staining and/or as gene amplification found on fluorescence in situ hybridization. pCR was defined as the absence of any invasive disease in the breast and the absence of micrometastasis or macrometastasis in the ipsilateral axillary lymph nodes.

Treatment

NST regimens comprised of anthracycline-taxane–containing regimens with a taxane (n = 261), anthracycline-based regimens without a taxane (n = 40), or single-agent taxane (n = 16). Anthracycline-containing regimens included three to six cycles of one of the following: fluorouracil (FU) 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2; FU 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2; FU 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2; or doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 intravenously (IV) on day 1 every 3 weeks. Taxanes coadministered with anthracyclines included paclitaxel 175 to 250 mg/m^2 or docetaxel 100 mg/m^2 IV on day 1 every 3 weeks for four cycles or paclitaxel 80 mg/m^2 IV weekly for 12 doses. Patients who were treated with a taxane as a single agent received four cycles of either docetaxel 60 to 100 mg/m^2 or paclitaxel 225 mg/m^2 as a 24-hour infusion at 3-week intervals. Of 60 patients who had HER2-positive breast cancer, 46 (77%) also received IV trastuzumab during NST.

After completion of NST, all patients underwent definitive breast surgery and axillary lymph node dissection or sentinel node dissection. The decision for or against breast-conserving surgery (BCS) was at the discretion of the patient and surgeon. Surgical intervention was BCS for 19% of patients (n = 61) and mastectomy for 81% of patients (n = 256). Postoperative radiation therapy was administered if patients had BCS, locally advanced disease at presentation, or inflammatory breast cancer. Patients who had hormone receptor–positive disease were offered 5 years of adjuvant endocrine therapy.

Statistical Analysis and Outcome Measures

The demographic and clinical characteristics were summarized and compared between the three groups, defined by *BRCA* status (noncarrier, *BRCA1* carrier, or *BRCA2* carrier), with the χ^2 test for categorical variables or Kruskal-Wallis test for continuous variables. χ^2 test or Fisher's exact test was used to identify the significant factors predictive of a pCR and to evaluate the impact of *BRCA* status on pCR in various patient subsets. A multivariate logistic regression model was fitted to examine the relationship between *BRCA* status and pCR, after adjusting for age, clinical tumor stage, ER status, nuclear grade, and use of trastuzumab with NST.

RFS was calculated from the time of initial diagnosis until the first date of documented disease recurrence or death or the date of last follow-up. OS was calculated from the time of initial diagnosis until the date of death from any cause or last follow-up. Survival outcomes were estimated using the Kaplan-Meier product-limit method and were tested for differences between groups by log-rank test. One exception is that while comparing OS and RFS between patient cohorts divided according to the surgery type and pCR achievement, time to event was estimated using landmark analysis, in which any events or censoring before surgery dates were excluded and were calculated from the date of NST response assessment (time of surgery) to event date or last follow-up date. Multicovariate Cox model was used to evaluate the effect of triple receptor– negative (TN) status on OS and RFS adjusting for other covariates. Because of the exploratory nature of the analysis, no adjustment on *P* value was made. *P* values $\leq$ .05 were considered statistically significant; all tests were two-sided. Statistical analysis was carried out using SAS 9.1.3 (SAS Institute, Cary, NC) and S-Plus 8.0 (Insightful Corporation, Seattle, WA).

RESULTS

Patient demographics, pretreatment clinical characteristics, and type of NST are summarized in Table 1. *BRCA* noncarriers tended to be older ($P = .03$) and were more likely to have N0 disease ($P = .03$), ER-positive ($P < .001$), PR-positive ($P = .001$), and HER2-positive ($P = .02$) tumors compared with *BRCA1* or *BRCA2* carriers. Tumor characteristics also differed between *BRCA1* and *BRCA2* carriers. *BRCA2* carriers had more frequently pretreatment N2-3 status (55%), and ER and PR positivity (91% and 62%, respectively). However, TN and nuclear grade 3 tumors were statistically more frequent in *BRCA1* carriers compared with *BRCA2* carriers and noncarriers. Other disease characteristics were not significantly different among the three groups.

Among the study population, the majority of patients (82%) received one of the anthracycline-taxane–containing regimens as NST. BCS was performed in 23% of patients in the noncarrier group versus 10% in the *BRCA1* group versus 4% in the *BRCA2* group ($P = .02$). Trastuzumab was administered in 42 (18%) of 237 of the noncarriers compared with two (4%) of 57 and two (9%) of 23 of the *BRCA1* and *BRCA2* carriers, respectively ($P = .01$).

Table 1. Patient Demographics and Baseline Disease Characteristics by *BRCA* Groups

Characteristic	*BRCA* non-carrier (n = 237) No.	%	*BRCA1* (n = 57) No.	%	*BRCA2* (n = 23) No.	%	*P*
Age, years							
Median	40		38		37		.03
Range	21-73		21-61		22-53		
Race							
White	182	76.8	43	75.4	16	69.6	.82
Black	13	5.5	2	3.5	1	4.3	
Hispanic	25	10.5	9	15.8	4	17.4	
Other	17	7.2	3	5.3	2	8.7	
Clinical tumor stage							
T1	27	11.6	6	10.5	5	21.7	.17
T2	132	56.7	29	50.9	12	52.2	
T3	43	18.5	13	22.8	1	4.3	
T4	18	7.7	7	12.3	5	21.7	
T4d	13	5.6	2	3.5	0	0	
Clinical nodal stage							
N0	73	32.0	14	25.0	2	9.1	.03
N1	93	40.8	24	42.9	8	36.4	
N2	24	10.5	4	7.1	7	31.8	
N3	38	16.7	14	25.0	5	22.7	
Clinical stage							
I	11	4.9	2	3.6	1	4.3	.31
II	125	55.3	27	48.2	9	39.1	
III	86	38.1	26	46.4	11	47.8	
IV	4	1.8	1	1.8	2	8.7	
ER status							
Negative	73	31.2	40	72.7	2	8.7	< .0001
Positive	161	68.8	15	27.3	21	91.3	
PR status							
Negative	110	47.2	42	77.8	8	38.1	.0001
Positive	123	52.8	12	22.2	13	61.9	
HER2 status							
Negative	170	75.9	46	92	19	90.5	.02
Positive	54	24.1	4	8	2	9.5	
Triple-negative status							
No	190	81.9	19	36.5	21	91.3	< .0001
Yes	42	18.1	33	63.5	2	8.7	
Histology							
Ductal	222	93.7	51	89.5	21	91.3	.38
Other	15	6.3	6	10.5	2	8.7	
Nuclear grade							
1	17	7.2	0	0	2	8.7	.002
2	86	36.6	10	18.5	11	47.8	
3	135	56.2	45	81.8	10	43.5	
Chemotherapy type							
Anthracycline-based regimen without a taxane	26	11.0	9	15.8	5	21.7	.41
AT	197	83.1	46	80.7	18	78.3	
Single-agent taxane	14	5.9	2	3.5	0	0	
Trastuzumab use							
No	193	82.1	55	96.5	21	91.3	.01
Yes	42	17.9	2	3.5	2	8.7	
Surgery type							
BCS	54	22.8	6	10.5	1	4.4	.02
Mastectomy	183	77.2	51	89.5	22	95.6	

Abbreviations: AT, anthracycline-taxane–containing regimens; BCS, breast-conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.

Response to NST

Overall, 82 patients (26%) achieved a pCR after NST. Median age at diagnosis was not significantly different between the pCR group (39.50 years; range, 21 to 61 years) and the non-pCR group (39.0 years; range, 22 to 73 years; $P = .56$). The pCR rate was significantly higher in *BRCA1* carriers (46%) compared with *BRCA2* carriers (13%) and noncarriers (22%; $P = .001$; Table 2). In univariate analysis, factors

Table 2. pCR Rates by Clinical Characteristics

Characteristic	No. of Patients	pCR No.	pCR %	*P*
Age, years				
≤ 50	280	71	25.4	.57
> 50	37	11	29.7	
Race				
White	241	58	24.1	.26
Black	16	4	25.0	
Hispanic	38	15	39.5	
Other	22	5	22.7	
Clinical tumor stage				
T1-3	268	68	25.4	.04
T4	30	6	20.0	
T4d	15	8	53.3	
Clinical nodal stage				
N0	89	20	22.5	.35
N1-3	217	60	27.6	
ER status				
Negative	115	46	40.0	< .001
Positive	197	35	17.8	
PR status				
Negative	160	55	34.4	< .001
Positive	148	26	17.6	
HER2 status				
Negative	235	49	20.9	< .001
Positive	60	27	45.0	
Triple-negative status				
No	230	53	23.0	.06
Yes	77	26	33.8	
Histology				
Ductal	294	72	24.5	.045
Other	23	10	43.5	
Nuclear grade				
1	19	2	10.5	.01
2	107	19	17.8	
3	186	59	31.7	
BRCA status				
Negative	237	53	22.4	< .001
BRCA1	57	26	45.6	
BRCA2	23	3	13.0	
Chemotherapy type				
Anthracycline-based regimen without a taxane	40	9	22.5	.75
AT	261	68	26.1	
Single-agent taxane	16	5	31.3	
Trastuzumab use				
No	269	59	21.9	.001
Yes	46	22	47.8	

Abbreviations: AT, anthracycline-taxane–containing regimens; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; pCR, pathologic complete response; PR, progesterone receptor.

Table 3. Multivariate Logistic Regression Model for Pathologic Complete Response

Variable	OR	95% CI	*P*
Age (n = 304)	1.01	0.98 to 1.05	.47
Clinical tumor stage			
T2 (n = 166) *v* T1 (n = 38)	0.63	0.27 to 1.47	.28
T3 (n = 56) *v* T1 (n = 38)	0.88	0.32 to 2.38	.80
T4 (n = 29) *v* T1 (n = 38)	0.42	0.12 to 1.49	.18
T4d (n = 15) *v* T1(n = 38)	1.87	0.49 to 7.15	.36
ER status, negative (n = 112) *v* positive (n = 192)	1.98	1.06 to 3.69	.03
Nuclear grade, 3 (n = 180) *v* 1/2 (n = 124)	1.56	0.82 to 2.99	.18
Trastuzumab use, yes (n = 45) *v* no (n = 259)	4.16	2.03 to 8.52	< .001
BRCA mutation, *BRCA1* (n = 54) *v* noncarriers (n = 227)	3.10	1.52 to 6.32	.002
BRCA2 (n = 23) *v* noncarriers (n = 227)	0.91	0.24 to 3.47	.89

Abbreviations: ER, estrogen receptor; OR, odds ratio.

associated with improved pCR rates were ER negativity ($P < .001$), PR negativity ($P = .001$), HER2 positivity ($P = .001$), nonductal histology ($P = .045$), pretreatment T4d status ($P = .04$), and higher nuclear grade ($P = .01$). The pCR rate was significantly higher in patients who received trastuzumab (48%) combined with NST compared with patients who did not (22%; $P = .001$).

In the multivariate logistic regression model, *BRCA1* status (odds ratio [OR] = 3.16; 95% CI, 1.55 to 6.42; $P = .002$), ER-negative status (OR = 1.96; 95% CI, 1.05 to 3.65; $P = .03$), and concurrent trastuzumab use with NST (OR = 4.18; 95% CI, 2.04 to 8.57; $P < .0001$) remained as independent significant predictors for a pCR (Table 3).

In the subset analyses, we found that *BRCA1* carriers who were treated with one of the anthracycline-taxane–containing regimens were more likely to achieve a pCR compared with *BRCA2* carriers and noncarriers (46% *v* 17% and 22%; $P = .005$); however, this did not reach a statistical significance in the multivariate analysis. In the subgroup of patients who did not receive concurrent trastuzumab with NST, *BRCA1* status was associated with a higher pCR rate (44%; $P = .001$). There were no significant differences in pCR rates among patients with TN breast cancer (n = 75) in relation to their *BRCA* status ($P = .62$; Table 4).

Survival Estimates

Median follow-up of all patients was 3.2 years (range, 0.5 to 21.6 years). *BRCA* status did not significantly influence the RFS ($P = .40$; Fig 1). The estimated 5-year RFS rate for the entire study cohort was 74% (95% CI, 68% to 81%), with 73% (95% CI, 67% to 81%) in the noncarrier group versus 72% (95%CI, 59% to 88%) in the *BRCA1* group versus 93% (95% CI, 80% to 100%) in the *BRCA2* group (Table 5).

Overall, patients who achieved a pCR had a better RFS than patients who did not (5-year rate, 93% [95% CI, 87% to 100%] *v* 68% [95% CI, 60% to 76%]; $P = .003$). Similarly, *BRCA1* carriers who achieved a pCR had better RFS compared with patients who did not (5-year rate, 95% [95% CI, 87% to 100%] *v* 53% [95% CI, 35% to 79%]; $P = .001$). In univariate analyses, T4/T4d status, TN status, PR negativity, and higher nuclear grade were associated with a significantly increased risk of recurrence. The patients who underwent BCS had better RFS rates when compared with the patients who underwent mastectomy (5-year rate, 87% [95% CI, 77% to 99%] *v* 71% [95% CI, 64% to 79%]; $P = .003$).

Likewise, *BRCA* status did not significantly influence the OS ($P = .33$; Fig 1). The 5-year OS estimates were 90% (95% CI, 86% to 96%) in the noncarrier group compared with 87% (95% CI, 77% to 98%) and 100% in the *BRCA1* and *BRCA2* groups, respectively (Table 5).

Patients who achieved a pCR had a better OS rate than patients who did not (5-year rate, 96% [95% CI, 91% to 100%] *v* 87% [95% CI, 81% to 93%]; $P = .04$). Among *BRCA1* carriers, patients who achieved a pCR had better OS than patients who did not (5-year rate, 100% *v* 75% [95% CI, 57% to 97%]; $P = .01$). In addition to the above noted prognostic features in the phenotype, ER negativity was also an independent predictor of increased risk of death. Moreover, patients who were treated with trastuzumab-containing NST regimens tended to have higher OS ($P = .07$). There were no differences in the OS estimates between the patients who underwent BCS versus mastectomy (5-year rate, 96% *v* 87%; $P = .09$).

In the multivariate analysis, TN status was associated with an increased risk of death (hazard ratio [HR] = 5.14; 95% CI, 2.39 to 11.05; $P < .001$) after adjusting for age and an increased risk of recurrence (HR = 2.20; 95% CI, 1.31 to 3.70; $P = .003$) after adjusting for age and tumor stage.

Table 4. Pathologic Complete Response Rate by *BRCA* Status in Patient Subgroups

Subgroup	*BRCA* Noncarrier			*BRCA1*			*BRCA2*			*P*
	No. of Patients	Total No.	%	No. of Patients	Total No.	%	No. of Patients	Total No.	%	
Trastuzumab use										
No	32	193	16.6	24	55	43.6	3	21	14.3	< .001
Yes	20	42	47.6	2	2	100	0	2	0	.24
Chemotherapy type										
AT	44	197	22.3	21	46	45.7	3	18	16.7	.005
Anthracycline-based regimen without a taxane	5	26	19.2	4	9	44.4	0	5	0	.19
Receptor status, triple negative	13	42	31.0	12	33	36.4	1	2	50	.62

Abbreviation: AT, anthracycline-taxane–containing regimens.

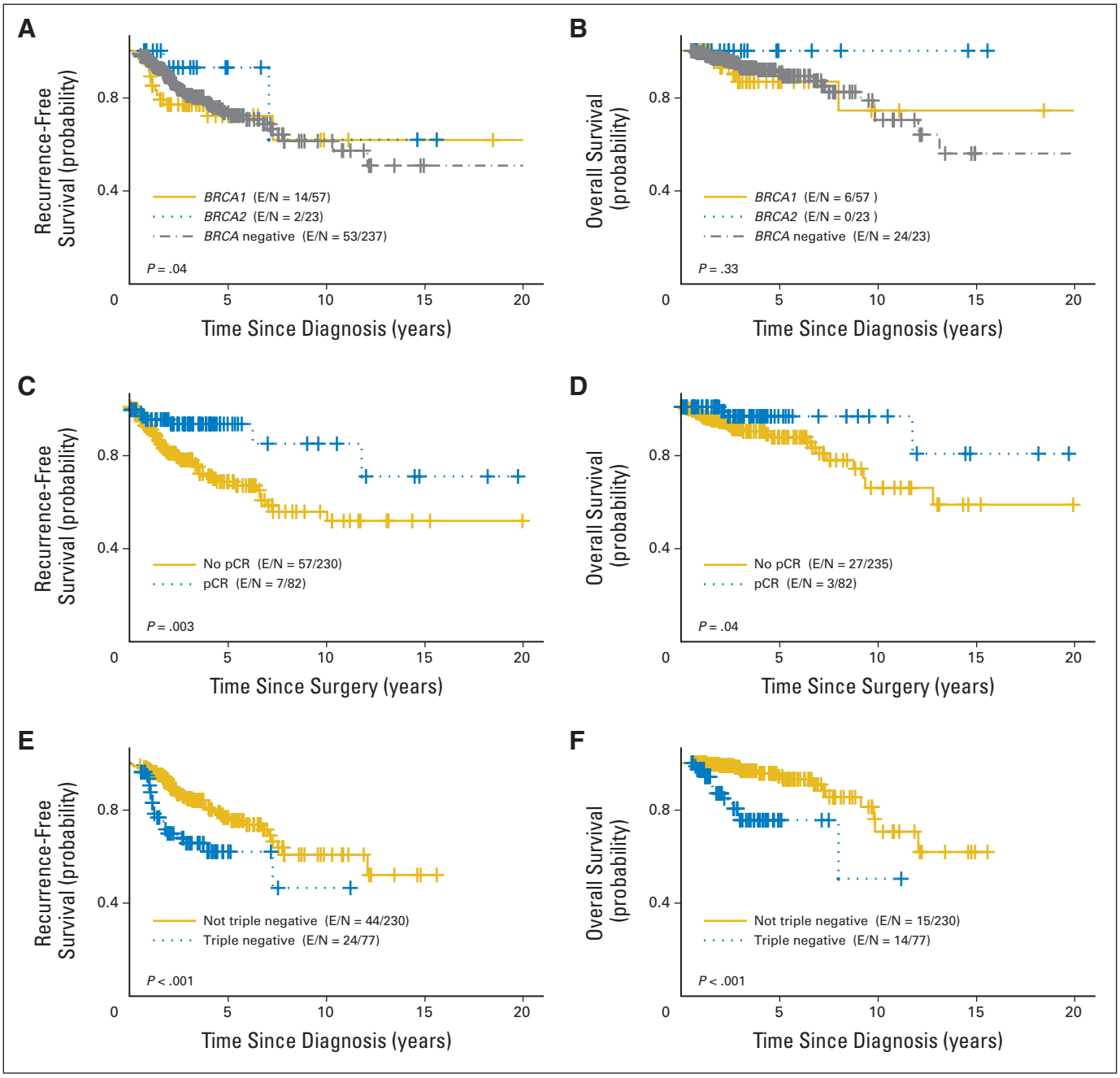

Fig 1. Kaplan-Meier estimates of recurrence-free survival (RFS) and overall survival (OS) by (A, B) *BRCA* status, (C, D) pathologic complete response (pCR), and (E, F) triple-negative status. E/N, events/number of patients.

To avoid potential ascertainment (Neyman) bias as a result of the long time interval between cancer diagnosis and genetic testing, we did an additional survival analysis on a subset of 224 patients who had their genetic counseling and testing within 12 months of their diagnosis. The distributions of clinical and pathologic characteristics were similar in this subgroup as compared with the entire series (data not shown). The pCR rate was significantly higher in *BRCA1* carriers (39%) compared with *BRCA2* carriers (12%) and noncarriers (21%; Fisher's exact test $P = .04$). In the multivariate logistic regression model, *BRCA1* status (OR = 3.12; 95% CI, 1.25 to 7.80; $P = .01$) remained as an independent significant predictor for a pCR. In addition, the median follow-up time was alike among the *BRCA1/2* carriers and noncarriers (median, 2.0 months; range, 0.7 to 8.2 months; and median, 2.7 months; range, 0.5 to 7.3 months, respectively). Both OS (5-year rate, 82% [95% CI, 68% to 98%] *v* 85% [95% CI, 77% to 95%] and RFS (5-year rate, 65% [95% CI, 47% to 89%] *v* 71% [95% CI, 61% to 82%] were not statistically different in the two groups ($P = .69$ and $P = .30$, respectively). In the multivariate analysis for this subset, TN status was still a significant predictor for both worse OS (HR = 6.66; 95% CI, 2.62 to 16.89; $P < .001$) after adjusting for age and worse RFS (HR = 2.65; 95% CI, 1.39 to 5.04; $P = .003$) after adjusting for age and tumor stage.

Table 5. Five-Year Overall Survival and Recurrence-Free Survival Estimates in Patient Subgroups

Variable	OS			RFS		
	%	95% CI	*P*	%	95% CI	*P*
Age, years						
≤ 50	88.9	84.2 to 93.9	.27	72.5	66.0 to 79.6	.54
> 50	100			85.9	73.6 to 100	
Race						
Black	82.5	62.8 to 100	.31	63.2	38.9 to 100	.43
Nonblack	90.8	86.5 to 95.2		74.9	68.9 to 81.4	
Clinical tumor stage						
T1-3	92.7	88.5 to 97.0	.16	78.6	72.4 to 85.4	< .001
T4	76.3	59.7 to 97.4		58.2	41.8 to 80.8	
T4d	84.4	66.6 to 100		43.6	24.0 to 79.2	
Clinical nodal stage						
N0	91.5	83.9 to 99.9	.46	83.5	73.9 to 94.3	.18
N1-3	89.8	84.7 to 95.2		72.0	64.8 to 79.9	
ER status						
Negative	82.6	74.8 to 91.2	.02	70.8	62.0 to 80.9	.18
Positive	94.7	90.2 to 99.5		75.2	67.5 to 83.9	
PR status						
Negative	85.9	79.6 to 92.7	.02	68.6	60.4 to 77.9	.01
Positive	94.4	88.9 to 100		78.3	69.7 to 87.9	
HER2 status						
Negative	87.1	81.4 to 93.2	.14	69.6	62.1 to 78.1	.11
Positive	97.0	91.3 to 100		81.2	69.6 to 94.7	
Triple-negative status						
No	94.4	90.2 to 98.7	< .001	76.7	69.8 to 84.2	< .001
Yes	75.4	64.4 to 88.4		62.0	50.0 to 76.7	
Nuclear grade						
1/2	95.7	91.7 to 100	.007	80.4	72.5 to 89.1	.03
3	85.3	78.2 to 93.1		68.2	59.5 to 78.1	
BRCA status						
Noncarrier	90.5	85.8 to 95.5	.33	73.5	66.6 to 81.0	.40
BRCA1	86.8	76.6 to 98.4		72.1	59.3 to 87.7	
BRCA2	100			92.9	80.3 to 100	
Chemotherapy type						
Anthracycline-based regimen without a taxane	94.1	86.5 to 100	.06	75.5	62.7 to 90.9	.63
AT	88.8	83.6 to 94.3		72.7	65.6 to 80.5	
Single-agent taxane	100			84.8	67.4 to 100	
Trastuzumab use						
No	88.9	84.3 to 93.9	.07	72.5	66.0 to 79.6	.17
Yes	100			85.2	73.7 to 98.5	
Surgery type						
BCS	95.8	90.1 to 100	.09	87.3	77.3 to 98.6	.003
Mastectomy	87.4	81.8 to 93.3		70.7	63.6 to 78.7	
pCR*						
No	87.0	81.3 to 93.1	.04	67.9	60.4 to 76.4	.003
Yes	95.9	90.6 to 100		92.7	86.7 to 99.2	

Abbreviations: AT, anthracycline-taxane–containing regimens; BCS, breast-conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; OS, overall survival; pCR, pathologic complete response; PR, progesterone receptor; RFS, recurrence-free survival.
*Calculated from surgery date.

DISCUSSION

Our data indicate that *BRCA1* status and ER negativity are independently associated with higher pCR rates after NST. Importantly, overall prognosis of breast cancer in *BRCA* carriers is similar to that of sporadic breast cancers, despite their identification with initial poor prognostic features. Our findings also suggest that TN *BRCA1* mutant cancers are just as sensitive to anthracycline-taxane–containing NST regimens as other high-grade TN breast cancers.

Consistent with the previous findings,[10,25] tumor histopathologic features were different in *BRCA1* carriers compared with *BRCA2* carriers and noncarriers. *BRCA1* carriers were more likely to have high nuclear grade and TN tumors than *BRCA2* carriers and noncarriers. Tumors from *BRCA2* carriers seemed to share similar pathologic characteristics with noncarriers, although they had a low frequency of HER2 protein overexpression. Although the *BRCA* carriers tended to present at a younger age and similar clinical stage of disease at initial diagnosis compared to noncarriers, the choice of NST did not differ between *BRCA* carriers and noncarriers, whereas mastectomy was more frequently performed in *BRCA* carriers than noncarriers.

Several studies have assessed the response rates to NST in *BRCA*-associated breast cancers, with reported pCR rates of up to 83%.[7,26-28] Confirming the previous observations, we demonstrated higher pCR rates in *BRCA1* carriers (46%) compared with noncarriers (22%). However, *BRCA2* carriers had a low pCR rate (13%). When other clinical and tumor characteristics were considered, the pCR rates also correlated significantly with T4d status, ER/PR negativity, HER2 positivity, nonductal histology, higher nuclear grade, and trastuzumab use. In multivariate logistic regression analysis, ER negativity, trastuzumab use, and *BRCA1* status remained as independent significant predictors for a pCR. Similar to other series,[29,30] we also found that the pCR rates in TN breast cancer *BRCA* noncarriers and TN breast cancer *BRCA1* carriers were similar, indicating that there may be some molecular and pathologic similarities between the TN and *BRCA1* mutant breast cancers. Alternatively, higher pCR rates observed in *BRCA1* carriers can be explained by the frequent association of TN tumors within this group.[6,7,31]

Few retrospective studies have examined the relative effectiveness of different chemotherapy regimens in the neoadjuvant setting of *BRCA*-associated breast cancers. In our study, there was a trend for higher pCR rates among *BRCA1* carriers who received anthracycline-taxane–containing regimens; however, this did not reach statistical significance in the multivariate analysis. These results suggest that *BRCA1* carriers are as sensitive to anthracycline- and taxane-containing regimens as are *BRCA* noncarriers. In contrast to our findings, Byrski et al[7] observed that women with a *BRCA1* mutation–positive breast cancer who received NST docetaxel in combination with doxorubicin were less likely to respond to the treatment than women with no mutation. More recently, at a subsequent analysis within the expanded study cohort of 102 patients with a *BRCA1* mutation, Byrski et al[28] observed the highest pCR rate among those treated with cisplatin (83%). These results are difficult to interpret because the baseline clinical and pathologic characteristics of the *BRCA1*-carriers and noncarriers are not identical.

In our study, the 5-year survival rates of 86% in *BRCA1* and 100% in *BRCA2* carriers were consistent with those of previous reports.[32-35] Although most studies show a similar prognosis for women with hereditary breast cancers compared with age-matched women with sporadic breast cancers,[34,36-40] other studies have reported worse survival outcomes.[41-43] Despite younger age at presentation, we found that the risk of breast cancer recurrence and death was similar between *BRCA* carriers and noncarriers in the first 5 years

after the initial diagnosis. The increased chemosensitivity of *BRCA*-related breast cancer tumors may explain why, despite a much higher prevalence of poor prognostic features, they show a similar prognosis. Furthermore, we demonstrate that the impact of pCR on survival outcomes remains significant in the subgroup of *BRCA1* carriers if pCR is achieved.

Several limitations must be considered when interpreting the results of our study. Our study was a retrospective analysis of women with breast cancer who were referred to genetic counseling services for testing of the *BRCA1* and *BRCA2* genes. Thus the *BRCA* noncarrier control group may not be a fair representation of sporadic cancers. Future studies that prospectively test for *BRCA* mutations in women treated with NST should be conducted to eliminate the possibility of selection bias. The small sample of *BRCA* carriers, in particular *BRCA2* carriers, in our study may have prevented statistically significant differences from emerging. In addition, patient selection for individual treatment regimens may have affected the differences in clinical outcome.

In conclusion, *BRCA1* status predicted response to NST in our cohort independent of baseline clinical and tumoral prognostic features and NST type. It is of considerable interest that higher pCR rates in *BRCA1* carriers could not be accounted for by differences in baseline prognostic factors, which have all been shown to correlate with pCR[44-46] and are known to be more prevalent in *BRCA* carriers as a group.[8] It is therefore tempting to speculate that it is the presence of the germline *BRCA1* mutation per se that is determining the difference in response to NST. Future studies with larger prospective cohorts and longer term follow-up are needed to validate these findings and to determine the optimum treatment for this subgroup of patients with breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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